CASE REPORT

Pyrexia of Unknown Origin: A High Suspicion of COVID-19

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ABSTRACT

We report a case of pyrexia of unknown origin (PUO) in a 19-year-old male, who was admitted with a history of pyrexia for 2 weeks. The diagnosis remained uncertain despite multiple investigations and the patient subsequently had various clinical manifestations similar to those seen in coronavirus disease 2019 (COVID-19). Since it was initially presumed to be pyrexia due to viral origin or enteric fever, patient was started on empirical treatment. The diagnosis of COVID-19 was confirmed by corroborating various biochemical markers that had a greater association with COVID-19. Patient was discharged after 21 days with empirical antibiotics, anticoagulants and other supportive medications. He required no further hospital admissions and has been on regular follow-up.

Keywords: Pyrexia of unknown origin, COVID-19, pyrexia, enteric fever, D-dimer, empiric

Pyrexia of unknown origin (PUO) is defined as fever ≥38.3°C (≥101°F) on at least two occasions, illness duration of ≥3 weeks and no known immunocompromised state.

The diagnosis remains uncertain after thorough history-taking, physical examination and the following obligatory investigations: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, total and differential leukocyte counts, hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase, ferritin, antinuclear antibodies and rheumatoid factor, protein electrophoresis, urinalysis, blood culture, urine culture, chest X-ray, abdominal ultrasonography (USG) and tuberculin skin test (TST) or interferon-γ release assay (IGRA).[1]

Coronavirus disease 2019 (COVID-19) is the latest crisis that has affected the world and it has challenged the leadership and health infrastructure worldwide. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began as an outbreak of pneumonia of unknown cause at a local seafood market in Wuhan, China. It soon spread globally and has since claimed over 6 million lives. It predominantly affected the middle-aged adults and elderly and males, though no gender or age group has been spared.[2]

The virus has a wide spectrum of symptoms due to the ability of the spike(S) protein to bind to the angiotensin-converting enzyme 2 (ACE2) receptors on various tissues. It spreads predominantly as a respiratory droplet infection from person to person.[3] Airborne transmission also occurs through aerosols. COVID-19 encompasses a spectrum of illness ranging from asymptomatic or presymptomatic, mild, moderate and severe to life-threatening critical disease. Most common symptoms are cough (53%), fever (43%), myalgia (36%), headache (34%), dyspnea (34%) and sore throat (20%).[4]

Gastrointestinal (GI) symptoms and dermatological manifestations are less common. Lab findings reveal lymphopenia, elevated CRP, transaminases, LDH, D-dimer, serum ferritin and troponin T.

The most common imaging findings are bilateral peripheral lower lung ground-glass opacities on high-resolution computed tomography (HRCT) chest. Reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal or oropharyngeal swab confirms the diagnosis.

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CASE REPORT

A young 19-year-old male from Hyderabad, India presented to St. Theresa's Multispeciality Hospital with a history of on and off high-grade fever for 10 days associated with chills and rigors. He also had altered bowel movements for 4 days. Bacterial infection, viral pyrexia, COVID-19, enteric fever were considered in the differential diagnosis and he was managed conservatively with antibiotics, antipyretics and other supportive medications. There was no history of loss of appetite, weight loss, night sweats, pain abdomen, rash, joint pain, chest pain, syncope, shortness of breath or burning micturition. He denied long-standing cough, headache, altered sensorium or blurred vision. There were no known comorbidities. His past medical history was unremarkable. He was an inter 2nd year student, and had been smoking for 1 year. He denied any family history, past history or contact history of tuberculosis (TB).

On examination, he had temperature of 101°F at the time of admission. His blood pressure (BP) was 100/80 mmHg, pulse 108 beats/min and respiration rate 18 breaths/min. There was no rash and lymphadenopathy. Cardiovascular and respiratory system examinations were unremarkable; abdominal examination revealed a soft and nontender abdomen. The neurological examination, including higher functions, was unremarkable. There were no features of meningism.

On admission, patient was started on normal saline, ringer lactate 100 mL/hour, IV antibiotic empirically after blood and urine samples sent for cultures. He was treated with proton pump inhibitors (PPI) and ondansetron and doxycycline was subsequently added to the treatment regimen. He continued to have high fever spikes, and his condition deteriorated. Complete blood count reveal hemoglobin - 14.4 gm, white blood count - 5,500 cu mm and platelets - 2,30,000. The D-dimer was 5,600 μg, serum creatinine - 1.27 mg, CRP level - 43.91 mg and ESR - 18 mm in first hour. His chest radiograph was unremarkable. His renal functions were normal. Liver function test (LFT) showed mild transaminitis with ALT - 73 U/L, AST - 86 U/L and serum bilirubin - 1.38 mg/dL. Blood culture and urine cultures were sterile. Widal titers were TH - 1:160, TO - 1:160, smear for malarial parasite and leptospirosis and brucellosis antibodies were negative. The Paul Bunnell test for infectious mononucleosis was negative. CT abdomen and HRCT chest were unremarkable; RT-PCR for COVID-19 and Mantoux test were negative. Electrocardiogram (ECG) showed normal sinus rhythm. 2D echocardiogram showed ejection fraction of 64%; there was no evidence of vegetation and clots. Bone marrow aspiration and biopsy were negative for TB, malignancy and other infections. He had continuous high-grade fever, vomiting, worsening of liver enzymes, elevated D-dimer levels; hence, antibiotics were escalated to carbapenems. His fever spikes gradually subsided, liver enzymes normalized, D-dimer reduced; the patient was symptomatically better and discharged in stable condition.

DISCUSSION

Pyrexia of unknown origin (PUO) has always been a challenge for the physicians. The principal concept of PUO, despite variations in definition, is that there is a significant fever that has persisted for longer than an acute self-limiting illness and that the disease has not been identified despite reasonable investigations in whatever setting is appropriate, either inpatient or outpatient.[5] Over the decades, many infectious, noninfectious, neoplastic and miscellaneous causes of PUO have been reported.[6] Given the extensive variety of possibilities, it is important to narrow down the etiologies by taking a thorough history and possible investigations to direct subsequent management.[7] In this case, the patient's fever persisted for 3 weeks, with raised inflammatory markers; all other possible tests were unremarkable. One of the highest possibilities was TB as countries outside the western nations have risk of up to 50%.[8]

As the Mantoux test was negative, some neglected diseases could have been scrub typhus, visceral leishmaniasis, brucellosis, among others.[9-11] Nevertheless, there were no physical or clinical evidences for such diseases. The new emerging disease was COVID-19 and despite RT-PCR being negative twice in this patient, the raised markers of CRP, D-dimer and ESR raised suspicion. Quite a few number of COVID-19 patients have been reported with no lung infections and its clinical signs, rather only with flu manifestations.[12]

COVID-19 pathological, physiological and diagnostic approaches are at the discovery stage. RT-PCR is the most widely used diagnostic test. However, Pu et al have reported false negative rates ranging from 6% to 12% in a recent study suggesting that PCR is not the perfect gold standard for comparison of diagnostic accuracy with COVID-19.[13]

In this study, we found raised CRP levels and studies have proved that elevated CRP can be used to predict the risk of disease progression in asymptomatic and/or

mild to severely ill persons.[12] CRP is a serum protein produced by hepatic endothelial cells that can be increased by a number of mediating factors, such as interleukin-6. It is becoming a prognostic marker of acute infection and also linked to chronic inflammation and heart diseases. Additionally, early plasma CRP growth has been proved to improve the chance of developing plasma leakage. Therefore, CRP levels could be used to anticipate chronic bronchitis caused by COVID-19.[14] Though there would seem to be plasma indicators linked to high levels of intensity and death in this regard, CRP thresholds were markedly elevated in seriously SARS-CoV-2 susceptible individuals.[15] One retrospective study revealed most individuals with acute stages of COVID-19 had considerably greater CRP levels than patients with non-acute illnesses (100 vs. 9.65 mg/L).[16] Another research in Vietnam reported all COVID-19 patients, regardless of illness stage, had a greater extent of CRP.[17]

In addition, in a Chinese study, people who died of COVID-19 had a higher CRP level (85.3 mg/L) than those who were improved and discharged (53.5 mg/L).[18] Furthermore, a study in the United States of America and Turkey stated that CRP tests are quick, easy and cost-consuming technique for estimating the amount of tissue damage in COVID-19 individuals.[19,20] Based on the studies, physicians may find that investigating the CRP level may be critical for early identification and adequate therapy of COVID-19-related problems. However, more large-scale investigations, are required to corroborate these findings.

Furthermore, we also found elevated D-dimer and ESR levels in the patient. Many studies have suggested the raised levels of the immunological, biochemical and hematological biomarkers as predictors of COVID-19 mortality.[21] D-dimer is one such marker, which contains two D fragments of the fibrin and is formed by the activation of the plasmin enzyme. This shows the presence of a demolished fibrin in the bloodstream and represents the activation of coagulation and fibrinolysis systems.[22] D-dimers are raised in patients of venous thromboembolism (VTE), cancers, inflammation, pregnancy and are most importantly used in clinical practice to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) and confirm the diagnosis of disseminated intravascular coagulation (DIC).[23] Furthermore, several studies have shown that COVID-19 predisposes patients to thrombosis, both in arteries and veins resulting in patient at risk for DVT, VTE and possible PE up to 25%.[24] D-dimer in COVID-19 infection can rise due to several reasons at various time points in infection. In addition to this, some underlying diseases such as cancer, diabetes, stroke and pregnancy may also trigger an increase in D-dimer levels in COVID-19 patients. One study has reported an increase in fibrinogen concentrations and D-dimer levels in the initial stages of COVID-19 and a three- to fourfold rise of D-dimer levels has been linked to poor prognosis of the patient.[25] Therefore, estimating the D-dimer levels and coagulation parameters from the initial stages of the disease can be helpful in controlling and managing of COVID-19 disease.

On the other hand, Zhang et al identified ESR as the most powerful factor to predict disease progression of COVID-19.[26] ESR is affected by the shape, size and concentration of red blood cells and plasma characteristics.[27] One study suggested that COVID-19 can change the form of erythrocytes or plasma characteristics along with the immune system via an unknown mechanism to increase the ESR levels.[28]

Moreover, the sustained elevated levels of ESR could damage the joints leading to joint diseases such as osteoarthritis, which can give negative effect on COVID-19 patients' prognosis. Besides, it may be a precursor of hepatic and renal dysfunction.[29] Accordingly, this emerging disease may influence the long-term prognosis of patients; however, it is difficult to predict the long-term prognosis of COVID-19 patients based on ESR alone. More cases and evidence are needed to address this issue.

Besides, our patient presented with fever with transaminitis, which is likely to be of viral etiology. Several studies stated that the levels of serum AST, ALT and LDH, which are liver function tests, were higher in severe COVID-19 patients when compared to the mild COVID-19 patients.[30,31] According to Onur et al, AST, ALT and LDH levels were higher in deceased COVID-19 patients than the survivors.[32]

Another study found that the ALT and AST levels were higher in severe patients than in non-serious patients.[33] These results indicated that severe liver dysfunction may have developed in those who have severe COVID-19 infection or died from the disease.

CONCLUSIONS

The diagnosis of COVID-19 in our patient was based on clinical and laboratory findings. Empirical treatment was given and symptomatically improved during the course in the hospital. Extensive laboratory evaluation along with detailed history and clinical examination are important to make diagnosis of PUO. COVID-19 can

present as fever of long duration even with RT-PCR testing negative; however, other biochemical markers always give a clue regarding the diagnosis.

Conflict of Interest Statement

The authors declare no competing interests.

Funding Source

Not applicable.

Ethics Approval

Ethical approval was not obtained for the publication of this case report because the report does not involve sharing of the personal details and personal photographs of the patient.

Authors' Contributions

AC, AB and SL examined and assessed the patient. AC and AB were involved in the management of the patient. SL and AB collected and analyzed data. SSP helped in guidance over compiling data, AC supervised the study. All the authors read and approved the final manuscript.

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Lung Volume Reduction Surgery vis-a-vis Bronchoscopic Lung Volume Reduction for Emphysema

Results of the CELEB (Comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement) trial presented at the concluding day of European Respiratory Society Congress 2022 in Barcelona show no differences in outcomes following lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) among patients with emphysema.[1]

Buttery et al compared the outcomes of LVRS and BLVR in this randomized-controlled single-blind superiority trial, which enrolled 88 patients with male preponderance (52%) and mean age of 64 years. There were 41 patients in the LVRS group and 47 in the BLVR group. The iBODE index composite score was used to evaluate the outcomes. The components of the iBODE index are body composition, airway obstruction, dyspnea and exercise capacity (incremental shuttle walk test).

At the end of the follow-up period of 1 year, the improvement in both intervention groups was equivalent as reflected by the i-BODE composite scores of –1.10 with LVRS and –0.82 with BLVR. The percentage predicted residual volume (RV% predicted) suggestive of air trapping in emphysema was –36.1 among patients who underwent LVRS versus –30.5 among those who underwent BLVR. Patient survival was also comparable with one death reported in each group.

This study designed as a superiority trial has for the first time compared the two interventions and concluded that the two procedures were comparable in outcomes (dyspnea, lung function and exercise capacity) and neither intervention was superior to the other with regard to safety and efficacy. Hence, not just clinicians, but patients with emphysema who are candidates for surgery, too can opt for BLVR in place of the more invasive lung volume reduction surgery as part of informed decision making. Noting these findings as "encouraging", the authors, however, advocate the need for larger trials to further examine the safety and effectiveness of the two procedures.

(Ref: [1]European Respiratory Society International Congress 2022. Abstract RCT44448. Buttery S. Comparative effect of lung volume reduction surgery for emphysema and bronchoscopic lung volume reduction with valve placement: the CELEB trial. Presented September 6, 2022. Available from: https://img.medscapestatic.com/article/980/491/Abstract_LVRS_BLVRS.pdf.)

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